ACT American College of Toxicology Signature Webinar

Impurities Safety Regulation–Q&A

October 20, 2021

Q: You speak exclusively for which there is legacy data and using M7's QSAR approach, what other approaches can be used to qualify an impurity?

David Woolley, PhD: In terms of where to get information/data on a substance's toxicity, there is a wealth of good data available online in databases such as the National Toxicology Program and PubChem as well as in the open literature. When choosing which data is appropriate make sure that it was conducted as close to the appropriate ICH guideline is as possible and has no "quirks" (unusual metabolic systems, unusual testing parameters or extraneous non-test substances present). Thresholds such as the TTC can be used but it's important to make sure the TTC is applicable for you test substance.

Q: What happens if the impurity that is positive in a QSAR is unstable and/or cannot be synthesized?

Amit Chaudhary, PhD: As per ICH M7guidance, for impurities that are not feasible to synthesize, bacterial mutagenicity testing may be carried out using a miniaturized assay format with justification and proven high concordance to the ICH-compliant assay.

For unstable impurities, appropriate spike/purge or purging factor studies may be performed in a manner representative of the commercial process, with a corresponding validated and fit-for-purpose analytical method. The acceptability of such assessment is reviewed by Chemists in Quality Discipline. Please refer to ICH M7 and Good ANDA Submission Practices Guidance for more information.

David Woolley, PhD: It would be important to understand the what the impurity degrades to and its relationship to the parent. The stability of the impurity should be understood in a biologically relevant media and the likely patient exposure.

Q: A M3 indication, with a mutagenic impurity (Ames positive) and is being controlled per M7. In humans, it's not found in human plasma, but seen in urine and feces sample ~ 2%. Is this metabolite a concern since it's not considered major metabolites and not seen in human circulation?

Amit Chaudhary, PhD: If the level of impurity exceeds qualification thresholds, then metabolite argument can be used for impurity qualification. Such justification should include qualitative and quantitative information showing that the plasma levels of the metabolite in vivo equals or exceeds the proposed clinical exposure levels at the maximum daily dose. The levels of metabolite in urine and feces are not acceptable to qualify an impurity as metabolite.

Alternatively, a general toxicity study considering the context of use of the drug product may be conducted to qualify the impurity, provided that doses used in the study provide adequate margins of safety.

Q: Suppose we have triester (3 acids are the same) as API and the metabolite is acid, can we assume that biester will be also metabolite? Do we need tox study for the biester?

Amit Chaudhary, PhD: For metabolite justification, qualitative information is not sufficient. The justification should include both qualitative and quantitative information showing that the plasma levels of the metabolite *in vivo* equals or exceeds the proposed clinical exposure levels at the maximum daily dose. Alternatively, a general toxicity study considering the context of use of the drug product may be conducted to qualify the impurity.

Q: If the impurity is a metabolite and we wish to qualify it by this approach - how can one bridge the exposure (AUC Cmax) in humans and derive from that a safe level in terms of % or mg?

Amit Chaudhary, PhD: In a pharmacokinetics study conducted appropriately considering the route of administration of the drug product, the comparison of area under the curve (AUC) or Cmax of the impurity as a metabolite *in vivo* and AUC or Cmax of the drug product should justify the proposed specification of the impurity.

Q: ICH Q3C PDEs have been calculated based upon adult body weight in nearly all cases I believe - if a product is intended for neonatal or pediatric populations, should PDEs be adjusted by body weight? And should additional research be conducted to identify possible pediatric toxicities in cases where an ICH Q3C limit is available?

David Woolley, PhD: The default value for weight in ICH Q3C is 50 kg. ICH Q3C states that “it is recognized that some adult patients weigh less than 50 kg; these patients are considered to be accommodated by the built-in safety factors used to determine a PDE. If the solvent was present in a formulation specifically intended for pediatric use, an adjustment for a lower body weight would be appropriate.”

One the key lessons we can take from of the study of neonate/pediatric/juvenile populations is that they are not just smaller adults. In such situations, as well adjusting for weight, I would look to see if there is any data available on difference in ADME (such as specific metabolizing enzymes, skin thickness (for dermal indications), absorption changes, etc.) between adults and the intended population then see how this could impact on the PDE value.

Dr. Chaudhary:

Q: What was the highest contents of DP impurities that you've seen justified and approved (e.g. >10%)? and what was the package for such safety assessment?

A: An impurity may be considered adequately qualified if the submitted justification supports the safety of the proposed clinical exposure and product quality is maintained.

In safety assessment, the impurity should be qualified for mutagenicity if it exceeds toxicological threshold of concern (TTC) and for both mutagenicity as well as general toxicity if it exceeds ICH Q3B qualification threshold. For mutagenicity evaluation, approaches described in ICH M7 guidance should be considered. For general toxicity evaluation, approaches described in ICH Q3B guidance should be considered. In cases, where the total daily intake of an impurity is greater than 1 mg/day and the proposed drug product is indicated for chronic use, additional genotoxicity, and general toxicity studies, as described in ICH Q3B, are needed.

Q: Are procedures for impurities identified in drugs already on the market different from those in R&D?

A: The approaches used to qualify impurities in a newly submitted generic drug application are similar to the impurity assessment in drugs that are already on the market. To qualify impurities in a generic drug, applicants may consider submitting toxicology data to support the safety of clinical exposures when safety thresholds are exceeded. Alternatively, applicants may also consider comparative impurity analysis to qualify the proposed limits.

Q: What are the common pitfalls associated with impurities evaluation in generic drugs? Can the methods and guidelines outlined by you be used in the evaluation of impurities in food products and cosmetics?

A: Please refer to the Good ANDA Submission Practices Guidance for Industry (https://www.fda.gov/regulatory-information/search-fda-guidance-documents/good-anda-submission-practices-guidance-industry). This guidance highlights common recurring deficiencies related to impurities assessments and provides recommendation to avoid common deficiencies.

The methods and guidelines outlined in the talk focused on drug substance and drug product-related impurities. Please refer to appropriate guidances for safety evaluation of impurities in food products and cosmetics.

Q: For a toxicology study to qualify an impurity, is the expectation to select a dose level of the drug at the lower end of the Dose Response curve (~ NOAEL) ; low enough to see an increase in the toxicity as a result of the higher level of the impurity in comparison, yet high enough to avoid seeing no toxicity at all?

A: A general toxicity conducted appropriately considering the clinical context of use of the drug product may be used to qualify an impurity. The no-observed-adverse-effect level (NOAEL) dose in such study should provide adequate margin of exposure as compared to the proposed clinical exposure.

Dr. Woolley:

Q: The problem with saying QSAR is unacceptable for general tox evaluation is that ALL assessment systems are fallible. Nothing should be used alone; together different systems give strength & confidence.

A: QSARs, like all assays and model, are not infallible. QSARs are tools to be used by toxicologists and it is important that such tools are used correctly. Understanding, how these fallibilities interact and how this relates to hazard identification and risk assessment is going to be a key area of toxicological interest in the next decade. Use of targeted computational analysis coupled with read across and a detailed understanding of the impurity and drug substance offers a valid alternative approach to in vivo and in vitro assays.